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Interaction between alcohol use and metabolic risk factors for liver disease: a critical review of epidemiological studies

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32

33 **Abbreviations**

34 ALT, alanine aminotransferase

35 AST, aspartate aminotransferase

36 BMI, body mass index

37 GGT, gamma-glutamyltransferase

38 HCC, hepatocellular carcinoma

39 MetS, metabolic syndrome

40 NAFLD, non-alcoholic fatty liver disease

41

43 **ABSTRACT**

44

45 Co-existence of alcohol use and metabolic risk – the two commonest population risk factors for
46 non-viral chronic liver disease – is a growing concern. Clinical and mechanistic evidence point to
47 considerable supra-additive interaction effects for the development and progression of chronic
48 liver disease between hazardous alcohol use and metabolic abnormalities including obesity,
49 diabetes, and the metabolic syndrome. Intermittent binge drinking once monthly or more often
50 seems to be associated with progression of liver disease even when average alcohol intake is
51 within the currently allowed limits for a diagnosis of non-alcoholic fatty liver disease (NAFLD),
52 and supra-additive interaction between binge drinking and the metabolic syndrome has been
53 reported. There are contradictory findings regarding the association between low alcohol use and
54 liver steatosis, but, clearly, the mechanisms of alcoholic hepatotoxicity extend beyond simple fat
55 accumulation. The presence of liver steatosis seems to amplify alcoholic hepatotoxicity. Recent
56 longitudinal studies of NAFLD subjects report low alcohol use associated with both increased
57 fibrosis progression and an elevated risk for liver cancer and severe liver disease. There is no clear
58 safe limit of alcohol intake in the presence of NAFLD or metabolic risk. The interaction effects
59 between alcohol and metabolic dysfunction merit increased attention in public health policy,
60 individual counseling, and risk stratification. Based on current evidence, a strict dichotomization
61 of liver disease into either pure alcoholic or non-alcoholic may be inappropriate.

62 **Introduction**

63 Chronic liver disease and its complications is a growing global public health burden. Worldwide,
64 liver cirrhosis is the 11th leading cause of death, and hepatocellular carcinoma is the 4th leading
65 cause of cancer death (Asrani et al., 2019).

66
67 Alcohol use and obesity and associated metabolic abnormalities are key independent population
68 risk factors for non-viral liver cirrhosis, hepatocellular carcinoma (HCC), and for prognosis in
69 established liver disease (Stepanova et al., 2010).

70
71 At the population level, there is an exponential dose-response relationship between alcohol
72 consumption and the risk for liver cirrhosis (Rehm et al., 2010; Thun et al., 1997; Askgaard et al.,
73 2015; Bellentani et al., 2000; Hagstrom et al., 2018). Both in general contexts (WHO, 2018) and in
74 liver-specific contexts (European Association for the Study of the Liver, 2016; Chalasani et al.,
75 2018), hazardous alcohol use is currently considered as a regular intake of more than 20 grams of
76 pure alcohol per day for women (140g/wk) or 30 grams for men (210g/wk), and these same
77 cutoffs have been used to separate alcoholic liver disease from non-alcoholic fatty liver disease
78 (NAFLD). However, the risk for liver cirrhosis begins to increase at alcohol consumption around
79 12-24 grams of alcohol per day or even lower, and no liver-safe limit of alcohol intake has been
80 firmly established (Roerecke et al., 2019; Rehm et al., 2010). Individual susceptibility to liver
81 toxicity from alcohol is wide and seems to depend on drinking pattern (binge drinking, drinking
82 outside meals), beverage type (lower risk for wine), gender, genetic and environmental factors,
83 diet, gut microbiome and co-morbidity.

84
85 Obesity, especially abdominal obesity, is associated with metabolic abnormalities and NAFLD
86 (Liu et al., 2010; Harris et al., 2017; Hagstrom et al., 2018; Caballeria et al., 2018) and is also a
87 co-factor in other types of liver diseases including alcoholic liver disease (Åberg et al., 2019;
88 Diehl and Day, 2017). NAFLD affects an estimated 25% of individuals in the general population,
89 and over 90% of those severely obese (Younossi et al., 2016), but less than 5% of NAFLD patients
90 eventually develop end-stage liver disease.

91
92 There is considerable overlap in the molecular pathways between alcoholic and non-alcoholic liver
93 disease, and the diseases share genetic risk factors and histologic features in common. Animal

94 studies have suggested synergism between the hepatotoxic effects of alcohol and high-fat diet-
95 induced obesity (Minato et al., 2014; Xu et al., 2011; Duly et al., 2015).

97 Currently around 23% of adults are obese, rising to 38% in the USA (OECD, 2017). Similarly, an
98 estimated quarter of the world's population suffers from the metabolic syndrome (MetS) (O'Neill
99 and O'Driscoll, 2015). Alcohol consumption in the population varies by region, but around 60% of
100 adults in Europe and the USA drink alcohol. When abstainers are excluded, average annual
101 consumption per capita among the actively drinking population is 15-17 litres of pure alcohol per
102 year (WHO, 2018). Therefore, many persons with obesity and/or metabolic disorders also
103 consume significant amounts of alcohol, and the synergistic interaction between them can
104 potentially have enormous impact on the population incidence of liver disease. In support of this,
105 we recently showed that 40% of cases of advanced non-viral liver disease in the general
106 population occurs in individuals with co-existent metabolic risk and regular alcohol intake, but
107 with a risk profile that does not fit either pure NAFLD or pure alcoholic liver disease (Åberg et al.,
108 2019b).

110 On the other hand, light alcohol consumption has been associated with improved insulin
111 sensitivity and lipid profile, inhibition of platelet activation, reduction of fibrinogen level, and
112 anti-inflammatory effects (Davies et al., 2002; Sierksma et al., 2004) possibly mediated through
113 phenol and polyphenol content in wine and beer (Gresele et al., 2011). This is substantiated by
114 some studies suggesting an association between low alcohol use and reduced prevalence of hepatic
115 steatosis (Gunji et al., 2009; Yamada et al., 2010; Moriya et al., 2011; Hiramane et al., 2011;
116 Hamaguchi et al., 2012; Dunn et al., 2012; Mitchell et al., 2018; Sookoian et al., 2014; Moriya et
117 al., 2015; Kwon et al., 2014; Hagstrom et al., 2017), but the evidence is conflicting and suffers
118 from methodological weaknesses. The recent Global Burden of Disease study concluded that the
119 level of alcohol consumption that minimizes health loss is zero (GBD 2016 Alcohol Collaborators,
120 2018).

122 The purpose of this critical review is to discuss the following aspects based on recently published
123 epidemiological and clinical evidence:

124 1) Does the combined effects of hazardous alcohol use and metabolic disorders increase the risk
125 for liver disease over and beyond the sum of their individual effects (supra-additive/synergistic
126 interaction) (Figure 1)?

127 2) Is there a safe, or even beneficial, level of alcohol use in persons with NAFLD or metabolic
128 dysfunction (Figure 1)?
129

130 **Methods**

131 For the purpose of this review, we conducted a search of the PubMed database and applied citation
132 chaining. For the first part, we included studies reporting interactions between hazardous alcohol
133 use ($>200\text{g/wk}$) and obesity or other metabolic factors for liver outcomes. As hazardous alcohol
134 intake usually represented the highest drinking category in these studies, we used the highest
135 drinking category when evaluating interaction effects. Regarding obesity, we concentrated on
136 body-mass index ($\text{BMI} \geq 30\text{kg/m}^2$) if this was reported. If alternative anthropometric measures
137 were reported, we also included these. From the relative risk estimates reported in the article, we
138 calculated attributable proportion due to interaction (Figure 1) according to Rothman (Rothman,
139 2002). For the second part (low alcohol use), we focused on studies analyzing clinically
140 meaningful liver outcomes (fibrosis, steatohepatitis, or clinical endpoints) in the presence of
141 baseline hepatic steatosis or metabolic risk. We relied on the definition of NAFLD used in the
142 various studies, which usually involved consumption below 20 grams of pure alcohol per day for
143 women and below 30 grams per day for men.
144

145 **Interactions between hazardous alcohol use and obesity in clinical studies**

146 We found 15 studies analyzing interactions between obesity and alcohol use for liver outcomes; 8
147 were cross-sectional (1 case-control) and 7 longitudinal (Table 1). The longitudinal studies all
148 used cohort methods and were mostly based on various population surveys, thus considered fairly
149 representative of the general population.
150

151 All studies analyzed obesity by BMI (Table 1). Only one study considered waist circumference in
152 addition to BMI (Åberg et al., 2018). BMI $<25\text{ kg/m}^2$ was used as the reference group in
153 interaction analyses in 8 of 15 studies; 3 studies used BMI $<30\text{ kg/m}^2$ as reference, one study used
154 BMI $25\text{--}27.4\text{ kg/m}^2$ (Yi et al., 2016), and 2 studies did not provide sufficient data for relative risks

155 compared to a reference group. Four studies explicitly stated to exclude underweight subjects from
156 the reference group. In interaction analyses, obesity was most often defined by a BMI ≥ 30 kg/m².
157

158 There was wide variation among studies in categorization of alcohol intake, both with regard to
159 the reference group and the highest consumption category (Table 1). Only 2 studies analyzed sex-
160 specific limits for alcohol intake (Åberg et al., 2018; Lau et al., 2015), and only 1 study explicitly
161 also analyzed binge drinking (Lau et al., 2015).
162

163 The outcome considered was abnormal liver enzymes in 5 studies, ultrasound-diagnosed steatosis
164 in 3, HCC in 3, liver mortality in 1, and a composite endpoint of liver-related hospital admission,
165 mortality (and HCC) in 3.
166

167 Supra-additive interaction between obesity and alcohol use was seen in 4 of 5 studies analyzing
168 liver enzymes (especially for gamma-glutamyltransferase (GGT)), and in 1 of 3 studies analyzing
169 steatosis. It should be noted that an elevated GGT may also reflect hazardous alcohol use without
170 liver injury (Niemelä and Alatalo, 2010). Of the 7 studies analyzing clinical liver outcomes, 5
171 found considerable supra-additive harmful effects between alcohol use and BMI, and additionally
172 1 study found such effects for waist circumference but not for BMI (Åberg et al., 2018). These
173 studies showing interaction were from England, Scotland, Finland and Taiwan. In contrast, Yi et al
174 (Yi et al., 2016) reported the highest risk of death from non-neoplastic liver disease in
175 underweight hazardous drinkers, and found no supra-additive interaction between obesity and
176 alcohol use compared to subjects with a BMI 25-27.4 kg/m² and alcohol use <9 g/wk. This South-
177 Korean study was restricted to men, relied on self-reported weights, defined obesity as a BMI
178 ≥ 27.5 kg/m², and excluded liver cancer mortality from the outcome (Yi et al., 2016). The lower
179 limit of alcohol intake in the highest drinking category was also relatively low (126 g/wk, based
180 on the study's definition of a standard drink).
181

182 In studies reporting supra-additive interaction, the fraction of risk attributable to interaction
183 between drinking and obesity varied between 26-88% for elevated liver enzymes, and between 25-
184 67% for clinical liver outcomes (Table 1). Lau et al (Lau et al., 2015) also reported supra-additive
185 interaction between obesity and binge drinking (at least 5 drinks per day at least 1 time during the
186 last month) for liver steatosis in men, but not in women.

187

188 **Interaction between hazardous alcohol use and other metabolic factors**

189 The association between obesity and liver disease is considered to be driven largely by associated
190 metabolic abnormalities, primarily insulin resistance (Gutierrez-Grobe et al., 2017; Ampuero et
191 al., 2018).

192

193 We found 5 studies (1 cross-sectional, 2 case-control and 2 longitudinal) that analyzed interactions
194 for liver-disease risk between alcohol and other metabolic factors than obesity; 3 analyzed
195 diabetes and 2 analyzed metabolic syndrome (Table 2). There was a profound interaction effect
196 between hazardous drinking and diabetes for the liver risk in all 3 studies, with estimates of
197 proportion attributable to interaction around 60-74% (Table 2). Park et al (Park et al., 2013)
198 reported supra-additive interaction between hazardous drinking and the metabolic syndrome for
199 GGT and aspartate aminotransferase (AST) elevation, and non-significantly so for alanine
200 aminotransferase (ALT). In our longitudinal population study (Åberg et al., 2017), we found a
201 supra-additive interaction effect between weekly binge drinking and presence of the MetS for
202 clinical liver outcomes (hospital admission, liver cancer or liver death) when adjusted for age and
203 average alcohol use (Figure 2).

204

205 In addition to these studies, Younossi et al (Younossi et al., 2019) reported supra-additive
206 interaction between hazardous alcohol use and the MetS for all-cause death in subjects with
207 baseline liver steatosis, based on the NHANES III survey. However, they found that the
208 interaction term between binge drinking and MetS was non-significant for all-cause death in these
209 subjects.

210

211 **Low alcohol intake in the presence of NAFLD and/or metabolic risk**

212 There are no randomized trials evaluating the effects of low alcohol intake in patients with
213 NAFLD. Several observational studies link light-moderate alcohol use, as compared to abstinence,
214 with a reduced risk for liver steatosis (Dunn et al., 2012; Mitchell et al., 2018; Sookoian et al.,
215 2014; Kwon et al., 2014; Hagstrom et al., 2017; Dixon et al., 2001). However, recent reviews
216 (Ajmera et al., 2017; Boyle et al., 2018) have raised several important methodological concerns
217 with these studies, including incomplete adjustment for confounders such as physical activity,
218 dietary factors, smoking, socioeconomic status and co-morbidity. The studies are mostly cross-

sectional and use surrogate endpoints such as steatosis or liver enzymes (Gunji et al., 2009; Yamada et al., 2010; Moriya et al., 2011; Hiramane et al., 2011; Hamaguchi et al., 2012; Sookoian et al., 2014; Moriya et al., 2015). The majority of these studies come from Japan, and ethnicity may influence alcohol metabolism and thereby modify alcoholic liver toxicity (Kourkoumpetis and Sood, 2019). In fact, the findings in the Japanese studies are in sharp contrast with those in some similar Western studies (Lau et al., 2015; Ruhl and Everhart, 2005; Suomela et al., 2015; Alatalo et al., 2008), and in contrast with longitudinal general population-based studies reporting increased risk for severe liver disease at alcohol intake even lower than 2 drinks/day (Rehm et al., 2010; Askgaard et al., 2015; Hagstrom et al., 2018; Åberg et al., 2018; Simpson et al., 2019; Sahlman et al., 2019). Simple liver steatosis or elevated liver enzymes may be poor outcome measures in population studies due to unclear prognostic relevance. We focus this part of our review on studies analyzing defined endpoints with acknowledged clinical relevance (steatohepatitis, fibrosis, or symptomatic liver disease), specifically in populations with NAFLD or metabolic risk. We found 17 such studies (10 cross-sectional, 7 longitudinal), summarized in Table 3.

Of 10 cross-sectional studies, 9 were based on selected patient populations from hospital clinics with biopsy-confirmed NAFLD or obese subjects undergoing bariatric surgery (Table 3). The population-based studies instead defined steatosis using ultrasound or specific indices (fatty liver index, hepatic steatosis index). The upper limit for low alcohol intake in these studies was typically set at ~20-30 g/day depending on the study.

Six studies stated explicitly how they treated former drinkers (current abstainers with previous drinking) (Dunn et al., 2012; Kwon et al., 2014; Dixon et al., 2001; Åberg et al., 2019a; Ascha et al., 2010; Ajmera et al., 2018), 6 stated how they treated binge drinkers (Dunn et al., 2012; Mitchell et al., 2018; Younossi et al., 2019; Åberg et al., 2019a; Ajmera et al., 2018; Ekstedt et al., 2009) and 5 evaluated lifetime drinking in their analyses (Dunn et al., 2012; Mitchell et al., 2018; Kwon et al., 2014; Hagstrom et al., 2017; Ajmera et al., 2018). Two studies had repeated measurements of alcohol use over time (Ajmera et al., 2018; Ekstedt et al., 2009), although these findings were not explicitly reported. There was a wide variation in the factors adjusted for in multivariate analyses (Table 3).

251 In cross-sectional clinical studies with liver histology, 2 (Dixon et al., 2001; Cotrim et al., 2009)
252 reported no independent effect of low alcohol intake on liver-disease severity, whereas 5 (Dunn et
253 al., 2012; Mitchell et al., 2018; Sookoian et al., 2014; Kwon et al., 2014; Hagstrom et al., 2017)
254 reported less severe liver disease with low alcohol intake compared to abstinence. Dietary factors
255 were poorly adjusted for in these studies.
256
257 Dunn et al (Dunn et al., 2012) reported lower odds of steatohepatitis (OR 0.56) and fibrosis (OR
258 0.56) among modest drinkers compared to lifetime abstainers. This study was based on patients
259 referred to specialized clinics participating in the NASH Clinical Research Network. Mitchell et al
260 (Mitchell et al., 2018) found less liver fibrosis in exclusive light wine drinkers, but not in
261 exclusive beer drinkers, compared to lifetime abstinent subjects. The association with reduced
262 liver fibrosis was not seen in subjects reporting binge drinking.
263
264 Furthermore, Hagström et al (Hagstrom et al., 2017) also found less liver fibrosis among those
265 reporting low alcohol consumption, but, somewhat paradoxically, they found an association
266 between elevated alcohol markers (phosphatidylethanol) and more liver fibrosis.
267
268 Wong et al (Wong et al., 2012) evaluated a population-based cohort of 922 subjects from Hong
269 Kong for liver steatosis and fibrosis by magnetic resonance spectroscopy and transient
270 elastography, respectively, and reported a weak direct correlation between alcohol use and
271 prevalent steatosis (non-significant in multivariate analysis), but no association with liver fibrosis.
272
273 In a recent longitudinal study with paired liver biopsies of NAFLD patients, Ajmera et al (Ajmera
274 et al., 2018) found low alcohol use (≤ 2 drinks/day) associated with lower odds of NASH
275 resolution compared with abstinence (OR 0.32) on adjusted analysis, and the drinkers exhibited
276 less reduction over time in steatosis grade and AST level. The study excluded former drinkers
277 from the abstinent group. These data provide strong evidence for liver harm from low alcohol use,
278 strongly challenging the cross-sectional studies above, although partly based on the same patients
279 (Dunn et al., 2012).
280
281 Ekstedt et al (Ekstedt et al., 2009) found binge drinking at least once monthly associated with
282 faster fibrosis progression in NAFLD.

283

284 A recent Mendelian randomization study categorized patients with NAFLD based on their
285 aldehyde dehydrogenase genotype to those prone to consume more or less alcohol (Sookoian et
286 al., 2016). The NAFLD patients genetically prone to drink less alcohol had less hepatic steatosis
287 and less features of steatohepatitis on histology compared to those prone to drink more alcohol,
288 which again suggests harmful effects of alcohol use in NAFLD.

289

290 In a large longitudinal Korean population cohort of 58 927 individuals with ultrasound-based
291 steatosis, Chang et al (Chang et al., 2019) found light to moderate alcohol intake associated with a
292 worsening of liver fibrosis over time based on non-invasive fibrosis markers. However, although
293 suitable for ruling out advanced fibrosis, these non-invasive fibrosis markers have a low positive
294 predictive value for fibrosis, and have not been validated for assessing change in fibrosis over
295 time. Age is a component in the scores used, and a rising score is thus, in part, a consequence of
296 aging itself. It therefore remains unclear whether the worsening in the fibrosis scores over time
297 truly reflect fibrosis progression.

298

299 Another longitudinal Japanese study of NAFLD patients from a specialized hepatology center
300 found increased HCC risk with increasing alcohol use, becoming significant at ≥ 40 g/day
301 (Kawamura et al., 2016).

302

303 We recently reported the findings from a large cohort study of 8345 individuals with hepatic
304 steatosis (fatty liver index >60) from the Finnish general population with linkage to nationwide
305 reliable registries for hard clinical endpoints (hospital admission, cancer, or death related to
306 advanced liver disease), and with adjustment for multiple acknowledged confounders and with
307 exclusion of former drinkers (Åberg et al., 2019a). In this study, the presence of steatosis at
308 baseline amplified the dose-dependent risk relationship between alcohol and incident liver disease.
309 Among subjects with baseline steatosis, we found no benefits from low alcohol intake with
310 regards to the risk for incident advanced clinical liver disease (Åberg et al., 2019a). Consuming
311 more than 10 g/day of alcohol increased the risk for liver disease in a dose-dependent fashion
312 regardless of the level of adjustment for confounders. One drink per day of non-wine beverages, or
313 2 drinks per day as wine, doubled the risk for advanced liver disease compared to lifetime
314 abstinence or minimal alcohol intake.

315

316 Extending these findings, among obese men in the general population with a waist-hip ratio in the
317 highest tertile, 1 daily alcohol drink yielded a similar relative risk for incident liver disease as 4
318 daily drinks in non-obese men (Figure 3) (Sahlman et al., 2019). This means that, in the presence
319 of marked abdominal obesity, hepatic toxicity of alcohol increases by a number of four.

320

321 Vilar-Gomez et al (Vilar-Gomez et al., 2018) found that, in patients with NAFLD-cirrhosis, low
322 alcohol use (<30 g/day for men and <20g/d for women) was associated with an increased risk of
323 death or liver transplantation (hazards ratio 2.3), hepatic decompensation (hazards ratio 1.7), and
324 HCC (hazards ratio 3.2) compared to abstinence, a finding that reinforces the need for absolute
325 alcohol abstinence in patients with cirrhosis. Two additional studies found an increased risk for
326 HCC among NAFLD patients with advanced fibrosis or cirrhosis reporting any alcohol use (Ascha
327 et al., 2010; Kimura et al., 2018).

328

329 **Extra-hepatic outcomes in NAFLD**

330 A J-shaped cardiovascular- and mortality benefit from low alcohol use in the general population is
331 widely reported (Di Castelnuovo et al., 2006), but has recently been questioned by the findings
332 from a robust meta-analysis (Wood et al., 2018).

333

334 A recent study in NAFLD patients with prospectively assessed alcohol consumption over time
335 found no association between low alcohol use and the presence of cardiovascular risk factors or
336 subclinical cardiovascular disease (VanWagner et al., 2017).

337

338 There are conflicting data regarding a J-shaped relationship between low alcohol use and all-cause
339 death in NAFLD cohorts in recent population-based studies (Younossi et al., 2019; Åberg et al.,
340 2019a; Hajifathalian et al., 2019). In our longitudinal population study, such a J-shaped
341 association between low alcohol use and all-cause death was only seen among never smokers, not
342 among current or former smokers (Åberg et al., 2019a). Alcohol intake more than 30 g/day was
343 associated with increased mortality in all NAFLD subjects.

344

345 Even low alcohol intake is associated with an increased risk for several types of cancer both in the
346 general population (Cao et al., 2015; Bagnardi et al., 2013) and in individuals with NAFLD
347 (Åberg et al., 2019a).

348

349 **Discussion**

350

351 *Interaction between hazardous alcohol use and metabolic risk*

352 The majority of studies report significant supra-additive interaction between hazardous alcohol use
353 and obesity for various liver outcomes including clinical ones (hospital admission due to liver
354 disease, liver cancer and liver-related death). Based on longitudinal studies with clinical liver
355 endpoints, approximately 50% of the excess risk for liver disease from the combination of
356 hazardous alcohol use and obesity is due to their interaction effects, whereas the remaining 50% is
357 due to the independent effects of alcohol and obesity. However, there was considerable variation
358 by study to the interaction estimate (range 0-67%), largely explained by methodological
359 differences. Alcohol, metabolic factors and their interactions may also affect the various liver
360 outcomes differently.

361

362 The synergistic interactions observed in these epidemiological studies are well in line with
363 mechanistic studies showing hepatotoxic effects from the combined exposure to alcohol and high-
364 fat diet above and beyond the sum of their individual effects (Minato et al., 2014; Xu et al., 2011;
365 Duly et al., 2015).

366

367 A number of caveats merit consideration when interpreting the epidemiologic findings. Many
368 studies failed to exclude former heavy drinkers from the reference group. Former drinkers may be
369 enriched with more co-morbidity and other factors affecting the choice to abstain from alcohol but
370 simultaneously raising the risk for liver disease (sick quitter bias). This may attenuate the observed
371 harm from alcohol in epidemiological studies.

372

373 Similarly, there seems to be a U-shaped association between BMI and incident liver outcomes
374 (Liu et al., 2010), where underweight might reflect liver disease or other form of illness. In
375 addition, in case-control studies where BMI is measured when the patient is already ill may not

376 reflect the person's usual weight. Prospective population cohort studies have an advantage in this
377 regard as BMI will generally reflect a healthy weight.

378

379 None of the longitudinal studies with clinical endpoints seems to have excluded both underweight
380 subjects and previous heavy drinkers from the reference group. If one were to apply these
381 exclusion criteria, the synergistic interaction would expectedly be even more pronounced.

382

383 BMI is an imperfect index for obesity when assessing risk for liver disease. Measures that better
384 reflect abdominal, also called visceral or central, adiposity, such as waist circumference and waist-
385 hip ratio (WHR), seem superior to BMI in predicting incident liver disease (Åberg et al., 2018;
386 Pang et al., 2015; Andreasson et al., 2017; Ioannou et al., 2005). The supra-additive interaction
387 effect also seems to become stronger when obesity is measured by the WHR (Sahlman et al.,
388 2019) or waist circumference (Åberg et al., 2018).

389

390 *Binge drinking*

391 Binge drinking, or heavy episodic drinking, is generally defined as drinking 60 gram alcohol or
392 more on one occasion at least once during the last month (WHO, 2018). Binge drinking has a
393 number of potentially harmful effects on the liver (Llerena et al., 2015), and has, for example,
394 been shown to induce insulin resistance that lasts even after blood alcohol levels become
395 undetectable (Lindtner et al., 2013). This contrasts to the improved insulin sensitivity associated
396 with low alcohol use.

397

398 Binge drinking habits may be neglected in studies assessing alcohol use through a quantity-
399 frequency approach, in which the respondent reports the frequency of drinking during a specific
400 time-period and, separately, the typical amount of alcohol consumed on the days that they drank.
401 This approach may fail to capture variations in drinking around a reported typical quantity, such as
402 with irregular binge drinking. For example, a person who drinks two drinks daily and a person
403 who drinks the same amount plus ten additional drinks on Saturday might report the same typical
404 quantity of two drinks per occasion. Thus, there is a need to explicitly address the issue of binge
405 drinking.

406

Binge drinking has been associated with NAFLD progression in both clinical and mechanistic studies (Llerena et al., 2015; Ventura-Cots et al., 2017). Binge drinking seems to counteract any potential benefit from low alcohol use in NAFLD (Mitchell et al., 2018), and the risk associated with binge drinking seems to arise at binge drinking episodes as infrequently as once monthly (Åberg et al., 2017; Younossi et al., 2019). Binge drinking emerged as a significant risk factor for liver disease only among those with the MetS, but not among those without it (Åberg et al., 2017). It could be speculated that a liver affected by steatosis may lack the capacity of a normal liver to recover after each episode of drinking during the break from alcohol intake. In support of this, animal studies show that intermittent alcohol administration serves as a “second hit” by aggravating hepatic oxidative stress and promoting steatohepatitis and fibrosis in mice with obesity-induced steatosis (Minato et al., 2014; Duly et al., 2015).

Low alcohol use in the presence of NAFLD or metabolic risk

Although cross-sectional studies report less liver fibrosis among NAFLD subjects with low alcohol use compared to complete abstinence, the findings are conflicting among studies, the potential benefit seems to be restricted to wine and non-binge drinking, and, most importantly, these findings have not been replicated in longitudinal studies. On the contrary, all longitudinal studies that analyzed specific histological or clinical liver outcomes report a tendency towards harm to the liver from low alcohol use, without any clear threshold effect.

A weakness of cross-sectional studies over longitudinal ones is that the predictor and outcome is measured at the same time, thereby limiting the ability to establish temporal relationship or causality. On the other hand, many longitudinal studies are unable to determine changes over time in the level of alcohol intake, or whether subjects develop additional risk factors over time.

A good example of the difference between cross-sectional and longitudinal analyzes are the studies by Dunn et al (Dunn et al., 2012) and Ajmera et al (Ajmera et al., 2018), which were in part based on the same patient population. Although both studies evaluated lifetime drinking and made careful efforts to exclude previous drinkers and binge drinkers and adjusted for multiple confounders, the cross-sectional study by Dunn et al (Dunn et al., 2012) found protective effects of low alcohol use, whereas the longitudinal study by Ajmera et al (Ajmera et al., 2018) reported harmful effects. Similarly, although low alcohol use has been found protective from steatosis in

439 numerous cross-sectional Japanese studies, the only longitudinal ones reported increased HCC risk
440 (Kawamura et al., 2016; Kimura et al., 2018).

441

442 Clinic-based studies with liver biopsies often had limited statistical power for multivariate
443 analyses, whereas many large population studies had limited availability of confounding variables,
444 thereby risking incomplete adjustment for relevant confounding, especially diet. It is well known
445 that individuals with low alcohol use tend to exhibit healthier dietary habits, healthier lifestyle,
446 higher socioeconomic status, and increased physical activity compared to complete abstainers
447 (Mukamal et al., 2006; Fillmore et al., 1998). These factors are difficult to fully adjust for in
448 observational studies. Such incomplete adjustment may exaggerate the protective effect of low
449 alcohol use in NAFLD.

450

451 Many studies adjusted the effect of alcohol for BMI. Alcohol use may cause obesity through
452 excess calories, and obesity is a risk factor for chronic liver disease. Therefore, some of the effects
453 of alcohol may be mediated through excess calories and obesity. Adjustment for BMI when
454 analyzing associations between alcohol and liver disease may hence lead to an over-adjustment
455 bias, i.e. subjects who consume more alcohol are more likely to gain weight, which in turn
456 increases their risk of liver disease. This tends to attenuate the observed risks from alcohol.

457

458 Failure to separate lifetime abstainers from current abstainers (previous alcohol use, currently quit
459 drinking) in many studies also leaves the potential for a sick quitter bias. Current abstainers may
460 be enriched with former heavy drinkers who present a more severe liver disease that actually
461 reflect irreversible alcoholic liver disease. Those with more severe liver disease may also be the
462 ones that choose to quit drinking as a consequence of disease, thereby entering the “non-exposed”
463 group.

464

465 There is concern for selection bias especially in clinic-based studies (Delgado-Rodriguez and
466 Llorca, 2004). Considering that the level of alcohol intake is itself involved in the definition of
467 NAFLD, filtering from clinical decision-making has already taken place when liver disease in a
468 patient with active alcohol use is categorized as NAFLD; this may result in a distorted spectrum of
469 baseline disease. Referral criteria of patients to liver clinics, recruitment to clinical studies, and the
470 number and characteristics of similar patients refusing study participation were often not clearly

471 specified. Survey-based general population studies have an advantage in this regard, as they do not
472 suffer the same selection bias inherent to clinic-based studies.

473

474 Alcohol intake was usually ascertained through the use of questionnaires, or in the clinical setting,
475 often by physician interviews. Such physician interviews have been shown to be less accurate in
476 discovering underlying alcohol risk use than cognitive lifetime drinking histories (Hayashi et al.,
477 2004).

478

479 Both intentional and unintentional underreporting of alcohol use is of major concern. Awareness
480 of a liver condition may lead to intentional underreporting of alcohol use by the patient in clinical
481 studies due to a fear that alcohol use will have a negative impact on the care provided. Indeed,
482 several studies suggest undetected significant alcohol use in many patients with hepatic steatosis
483 labeled as NAFLD (Hagstrom et al., 2017; Hayashi et al., 2004; Staufer et al., 2019). Again,
484 prospective population-based studies have an advantage over clinic-based studies, since healthy
485 participants are more likely to respond honestly, and study subjects are often unaware of having
486 steatosis when it is defined by specific laboratory indices such as the fatty liver index.

487

488 Unintentional underreporting of alcohol use is also a concern. It is difficult for anyone to
489 accurately quantify a unit of alcohol, especially as serving size and alcohol content within and
490 across beverage type may vary considerably. Quantification of alcohol intake typically relies on
491 recall of past drinking, for instance during the last year, with a significant risk for recall bias
492 (Stockwell et al., 2004). Underreporting alcohol use tends to increase as risk drinking behaviors
493 increases, but this is complex and inconsistent (Isted et al., 2015). A general underreporting of
494 alcohol intake might overestimate the level of alcohol intake needed to induce liver harm, but
495 underreporting may also be skewed rather than general, whereby the net effect becomes less
496 predictable.

497

498 **Suggestions for future research**

499 A key limitation with current longitudinal studies is that alcohol intake is usually assessed only at
500 one point in time. There is a need for large longitudinal population-based studies that measure
501 alcohol intake at several time points to assess the impact of changes over time in alcohol use
502 patterns.

503

504 Given that underreporting of alcohol use generally increases together with increasing alcohol use,
505 and that hazardous alcohol use can contribute to weight gain, potentially there may be more
506 underreporting of alcohol use in the obese group than in non-obese groups. Therefore, some of the
507 interaction effect between obesity and hazardous alcohol use could actually represent the effect of
508 unmeasured alcohol intake. To overcome this uncertainty related to questionnaire-based
509 ascertainment of alcohol use, there is a need for studies quantifying alcohol intake by sensitive and
510 specific biomarkers such as phosphatidylethanol (Viel et al., 2012).

511

512 More study is also needed on how to best incorporate the interaction effects between alcohol and
513 metabolic risk in clinically useful risk stratification strategies. More data is needed on which
514 specific obesity-related metabolic components drive these harmful interaction effects for liver
515 disease. Factors influencing individual susceptibility to alcohol toxicity, including genetics, also
516 deserve further study.

517

518 It seems that binge drinking is associated with progression of liver disease even when average
519 alcohol consumption is within the currently allowed limits to receive a NAFLD diagnosis. Binge
520 drinking probably warrants explicit consideration when designing drug trials in NAFLD, and
521 should be incorporated in the diagnostic criteria of NAFLD.

522

523 **Conclusions**

524 Although not entirely consistent, current epidemiologic and clinical evidence point to considerable
525 supra-additive interaction for the risk of liver disease between hazardous alcohol use and
526 metabolic abnormalities including obesity, diabetes and the MetS. This merits increased attention
527 in disease prevention, risk stratification, and individual counseling.

528

529 There is no clear safe limit of alcohol intake in the presence of NAFLD or metabolic risk. The
530 presence of steatosis seems to amplify alcoholic liver toxicity. Recent studies based on unselected
531 population cohorts of subjects unaware of having steatosis with longitudinal follow-up for clinical
532 liver outcomes, and with comprehensive adjustment for confounders, report low alcohol use being
533 associated with an elevated risk for incident liver disease. However, in individuals with NAFLD

534 without advanced liver fibrosis, the absolute risk increase from maximum 1 daily standard glass of
535 wine (10g of ethanol) seems small.

536

537 Although low alcohol use might ameliorate insulin resistance and thereby possibly reduce hepatic
538 steatosis, alcohol's numerous detrimental effects extend well beyond simple fat accumulation, and
539 the net effect seems to be harmful already at low doses. There is no clinical evidence to support
540 that low alcohol would protect from symptomatic liver disease. In NAFLD with advanced liver
541 disease or particular risk for progressive liver disease, complete alcohol abstinence is advised.

542

543

544

545

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864

865 FIGURE LEGENDS

866

867 Figure 1. The concept of interaction between alcohol and obesity for the risk of liver disease.

868 Obesity and metabolic risk may modify the effects on the liver of low alcohol use (<1-3

869 drinks/day), with some studies reporting harm and other studies reporting benefits from low

870 alcohol use compared to abstinence. Regarding hazardous alcohol use, studies suggest supra-

871 additive interaction effects between exposure to alcohol (R_{alco}) and obesity (R_{obe}), so that the

872 combined risk effect of having both exposures (R_{combi}) is higher than the sum of their individual

873 risk effects ($R_{alco} + R_{obe}$).

874

875 Figure 2. Hazards ratios for the contribution of weekly binge drinking, the metabolic syndrome

876 (MetS), and their combination (interaction) to the risk for incident clinical liver disease in

877 comparison to subjects without the MetS who reported no binge drinking or binge drinking less

878 often than once monthly (baseline risk) in the Finnish Health 2000 study. The attributable

879 proportion due to interaction in this example is 29% $((4.61 - 2.26 - 2.03 + 1) / 4.61 = 0.29)$.

880 (Reprinted with permission from Åberg F et al. Binge drinking and the risk for liver events: A

881 population-based cohort study. *Liver International* 2017;37:1373 (Åberg et al., 2017).

882

883 Figure 3. Interaction between average alcohol intake (grams of ethanol per week) and waist-hip

884 ratio for the risk of incident clinical liver disease among men in the Finnish general population.

885 (Reprinted with permission from Sahlman P et al. Genetic and lifestyle risk factors for advanced

886 liver disease among men and women. *Journal of Gastroenterology and Hepatology* 2019 (Sahlman

887 et al., 2019).

Table 1. Studies analyzing interaction between hazardous alcohol use and obesity for various liver outcomes.

Author, year	Country	Study design	Study subjects	Outcome measure	Categories	Findings	Adjustments	Supra-additive interaction	Attributable proportion
Liver-function tests									
Ruhl, 2005	USA	Cross-sectional	13 580 men and women recruited in 1988-1994 (NHANES III)	Elevated ALT or AST	Reference: BMI <25 kg/m ² + nondrinker Drinker: ≥2 drinks/d Obese: BMI ≥30 kg/m ²	Obese OR 2.1 Drinker OR 1.6 Obese drinker OR 5.4	Age, sex, ethnicity, smoking, caffeine consumption, HbA1c	Yes	50%
Alatalo, 2008	Finland	Cross-sectional	2 164 apparently health men and women recruited in a survey to establish enzyme reference intervals in the Nordic countries	Elevated ALT, AST or GGT	Reference: BMI 19-24.9 kg/m ² + abstainer Drinker: 0-280 g/wk Obese: BMI ≥30 kg/m ²	Relative differences (%) in mean levels compared to reference group			
						ALT: obese +52% Drinker +5% Obese drinker +105%	-	Yes	
						AST: obese +18% Drinker +5% Obese drinker +41%	-	Yes	
						GGT: obese +36% Drinker +18% Obese drinker +123%	-	Yes	
Adams, 2008	Australia	Cross-sectional	2 610 men and women, 20-80yrs, residing in Busselton recruited in 1994 for a health	Elevated ALT or GGT	-	Numbers not given for calculation	Age	No	

			survey						
Loomba, 2009	USA	Cross-sectional	2 364 men and women, mean age 70 yrs, recruited in 1984-1987 (Rancho Bernardo Study)	Elevated ALT	Reference: BMI 18.5-24.9 kg/m ² + nondrinker Drinker: >210 g/wk Obese: BMI ≥30 kg/m ²	Obese OR 1.4 Drinker OR 2.1 Obese drinker OR 8.9	Age, sex, total cholesterol, serum triglycerides, fasting plasma glucose, systolic blood pressure, diabetes	Yes	72%
				Elevated AST	Reference: BMI 18.5-24.9 kg/m ² + nondrinker Drinker: >210 g/wk Obese: BMI ≥30 kg/m ²	Obese OR 1.3 Drinker OR 2.3 Obese drinker OR 21	Age, sex, total cholesterol, serum triglycerides, fasting plasma glucose, systolic blood pressure, diabetes	Yes	88%
Shen, 2010	China	Longitudinal	500 men and women with normal liver tests and without liver disease recruited in 1999 for an epidemiological survey in Zhejiang Province,	Elevated ALT or GGT	Reference: BMI <25 kg/m ² + alcohol use <280 g/wk Drinker: ≥280 g/wk Overweight/obese: BMI ≥25 kg/m ²	Overweight/obese RR 1.40 (0.84-2.33) Drinker RR 2.20 (1.38-3.50) Overweight/obese drinker RR 3.49 (2.24-5.43)	-	Yes	26%

			follow-up 7 yrs						
Steatosis									
Bellentani, 2000	Italy	Cross-sectional	257 men and women recruited in 1997 (Dionysos study)	Steatosis on US	Reference: BMI <25 kg/m ² + alcohol use <210 g/wk and lifetime alcohol use <100kg Drinker: ≥420 g/wk or lifetime use ≥100kg Obese: BMI >30 kg/m ²	Obese RR 4.6 (2.5-11.0) Drinker RR 2.8 (1.4-7.1) Obese drinker RR 5.8 (3.2-12.3)	-	No	
Lau, 2015	Germany	Cross-sectional	4 009 men and women (The Study of Health in Pomerania)	Steatosis on US	MEN Reference: BMI <25 kg/m ² + current abstainers Drinker: ≥420 g/wk Obese: BMI ≥30 kg/m ² WOMEN Reference: BMI <25 kg/m ² + current abstainers Drinker: >140 g/wk Obese: BMI ≥30 kg/m ²	MEN Obese ? (data not given) Drinker OR 21.5 Obese drinker OR 101.6 WOMEN Obese ? (data not given) Drinker OR 0.15 Obese drinker HR 3.30	Age, HbA1c	Yes	?
					BINGE Reference: BMI <25 kg/m ² + nonbinge drinking Binge drinker: ≥5 drinks/d ≥1 time during the last month Obese: BMI ≥30 kg/m ²	MEN Obese OR 8.96 Binge drinker OR 2.73 Obese binge drinker OR 14.10 WOMEN Obese OR 7.31 Binge drinker OR 1.69 Obese binge drinker OR 7.71	Age, HbA1c, average daily alcohol use	MEN: Yes, WOMEN: No	MEN 24%
Takahashi,	Japan	Cross-	8 029 men and	Steatosis		Highest prevalence of	-	No	

2015		sectional	women, mean age 50 yrs, undergoing general health examination at 3 health centers recruited in 2009-2010	on US		steatosis in obese (BMI >30 kg/m ²) low-drinking (<140 g/wk) men and obese (BMI >30 kg/m ²) heavy-drinking (>350 g/wk) women			
Clinical outcomes									
Marrero, 2005	USA	Case-control	70 with HCC and 70 with liver cirrhosis without HCC recruited in 2002-2003 from hospital clinics	HCC	Reference: BMI <30 kg/m ² + alcohol use <100 drinks per lifetime Drinker: ≥100 drinks per lifetime Obese: BMI ≥30 kg/m ²	Obese OR 1.2 (1.4-17.3) Drinker OR 2.6 (1.8-7.6) Obese drinker OR 5.5 (1.8-20)	-	Yes	49%
Loomba, 2010	Taiwan	Longitudinal	2 260 Taiwanese hepatitis B-positive men recruited in the REVEAL-HBV study, follow-up 14 yrs	HCC	Reference: BMI <30 kg/m ² + nondrinker Drinker: alcohol use ≥4 d/wk for ≥1yr Obese: BMI ≥30 kg/m ²	Obese HR 0.64 (0.16-2.63) Drinker HR 1.64 (1.12-2.40) Obese drinker HR 3.40 (1.24-9.34)	Age, ALT, HBV-DNA, baseline cirrhosis	Yes	62%
Loomba, 2013	Taiwan	Longitudinal	23 712 Taiwanese residents	HCC	Reference: BMI <30 kg/m ² + nondrinker Drinker: alcohol use ≥4 d/wk for	Obese HR 1.17 (0.65-2.11) Drinker HR 1.46 (1.07-1.98)	Age, sex, smoking, ALT, HBsAg, anti-HCV	Yes	67% (unadjusted as reported)

			recruited in 1991-1992 (cancer screening program), mean follow-up 11.6 yrs		≥ 1 yr Obese: BMI ≥ 30 kg/m ²	Obese drinker HR 3.82 (1.94-7.52)	antibodies, diabetes		by the authors), 57% (calculated based on adjusted HRs)
Liu, 2010	England and Scotland	Longitudinal	1 230 662 middle-aged women (Million Women Study) recruited in 1996-2001, mean follow-up 6.2 yrs	Liver-related hospital admission or death	Reference: BMI 22.5-25 kg/m ² + alcohol use <70 g/wk Drinker: ≥ 150 g/wk Obese: BMI ≥ 30 kg/m ²	Obese RR 1.35 (1.15-1.59) Drinker RR 3.44 (2.70-4.37) Obese drinker RR 6.53 (4.98-8.55)	Age, recruitment region, alcohol use, smoking, socioeconomic status, physical activity	Yes	42%
Hart, 2010	Scotland	Longitudinal	9 559 men aged 18-92 yrs (Midspan and Collaborative studies) recruited in 1965-1968 and 1970-1973, median follow-up 29 yrs	Liver mortality	Reference: BMI <25 kg/m ² + alcohol use <120 g/wk Drinker: ≥ 120 g/wk Overweight/obese: BMI ≥ 25 kg/m ²	Overweight/obese RR 1.29 (0.60-2.80) Drinker RR 3.66 (1.74-7.71) Overweight/obese drinker RR 9.53 (4.98-18.2)	Age, study, social class, smoking, height, bronchitis, FEV1, angina, ischemia on electrocardiogram, diabetes	Yes	59%
Yi, 2016	South	Longitudinal	101 735 men	Liver	Reference: BMI 25-27.4 kg/m ² +	Overweight/obese HR 2.8	Age, smoking	No	

	Korea		recruited in a postal survey 2004 (Korean Veterans Health Study), follow-up 6 yrs	mortality (liver cancer excluded)	alcohol use <9 g/wk Drinker: ≥ 126 g/wk Overweight/obese: BMI ≥ 27.5 kg/m ² *	Drinker HR 1.3 Overweight/obese drinker HR 3.6 (highest risk in underweight drinkers, BMI <21, HR 12.7) *	status, physical activity, household income		
Åberg, 2018	Finland	Longitudinal	6 732 men and women, mean age 54 yrs, recruited in 2000-2001 (Health 2000 Study), mean follow-up 11.4 yrs	Liver-related hospital admission, cancer or death	BMI Reference: BMI <25 kg/m ² + alcohol use <210g/wk for men and <140g/wk Drinker: above these sex-specific limits Obese: BMI >30 kg/m ²	Obese HR 1.48 Drinker HR 5.84 Obese drinker HR 4.06	Age, sex	No	
					WC Reference: WC <102 cm + alcohol use <210g/wk for men and WC <88cm + alcohol use <140g/wk for women Drinker: above these sex-specific limits Obese: WC above these sex-specific limits	Obese HR 1.46 Drinker HR 4.55 Obese drinker HR 6.72	Age, sex	Yes	25%

* Calculated from a subset of 72 152 subjects without baseline liver disease and without viral hepatitis

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; OR, odds ratio; GGT, gamma-glutamyltransferase; BMI, body mass index; RR, risk ratio; HR, hazards ratio; US, ultrasound; HCC, hepatocellular carcinoma; WC, waist circumference

Table 2. Studies analyzing interaction between hazardous alcohol use and metabolic factors other than obesity for various liver outcomes.

Author, year	Country	Study design	Study subjects	Outcome measure	Categories	Findings	Adjustments	Supra-additive interaction	Attributable proportion
Park, 2013	South Korea	Cross-sectional	5 946 men and women recruited in 2003-2010 (Korean National Cancer Center Cohort)	Elevated ALT, AST or GGT	Reference: No metabolic syndrome + alcohol abstainer Drinker: ≥ 24 g/day Metabolic syndrome: yes (Adult Treatment Panel III)	GGT ≥ 30 U/L: Metabolic syndrome OR 1.79 (1.21-2.66) Drinker OR 7.81 (6.07-10.06) Metabolic syndrome + drinker OR 13.43 (8.35-21.60)	Age, gender, education level, smoking status	Yes	36%
						ALT ≥ 40 U/L: Metabolic syndrome OR ? Drinker OR 1.61 (1.00-2.60) Metabolic syndrome + drinker OR 3.88 (2.00-7.55)	as above	Yes, but non-significant	?
						AST ≥ 40 U/L: Metabolic syndrome OR ? Drinker OR 3.73 (2.54-5.47) Metabolic syndrome + drinker OR 6.42 (3.64-11.35)	as above	Yes	?
Hassan, 2002	USA	Case-control	115 men and women with hepatocellular carcinoma and 230 matched controls with other malignancies recruited in 1994-	HCC	Reference: No diabetes + alcohol use < 439 g/wk Drinker: > 439 g/wk Diabetes: yes	Diabetes OR 2.4 (1.3-4.5) Drinker OR 2.6 (1.4-4.9) Diabetes + drinker OR 9.9 (2.5-39.3)	HBsAg, anti-HCV antibodies, smoking status	Yes	60%

			1995 at a single center						
Yuan, 2004	USA	Case-control	295 men and women with hepatocellular carcinoma recruited in 1984-2002 from a population-based cancer registry and 435 matched healthy neighborhood control subjects	HCC	Reference: No diabetes + alcohol use ≤ 4 drinks/d Drinker: >4 drinks/d Diabetes: yes	Diabetes OR 2.5 (1.5-4.0) Drinker OR 3.4 (2.2-5.4) Diabetes + drinker OR 17.3 (3.9-77.6)	Age, sex, race, education level, smoking status	Yes	72%
Åberg, 2018	Finland	Longitudinal	6 732 men and women, mean age 54 yrs, recruited in 2000-2001 (Health 2000 Study), mean follow-up 11.4 yrs	Liver-related hospital admission, cancer or death	Reference: No diabetes + alcohol use <210 g/wk for men and <140 g/wk for women Drinker: above these sex-specific limits Diabetes: yes	Diabetes HR 2.58 Drinker HR 3.56 Diabetes + drinker HR 19.5	Age, sex	Yes	74%
Åberg, 2017	Finland	Longitudinal	6 366 men and women, mean age 54 yrs, recruited in 2000-2001 (Health 2000 Study), mean follow-up 11.4 yrs	Liver-related hospital admission, cancer or death	Reference: No metabolic syndrome + no binge drinking or less than once monthly Binge drinking: ≥ 60 g/occasion at least weekly Metabolic syndrome: yes (Joint Interim Statement	Metabolic syndrome HR 2.03 (1.18-3.47) Weekly binge drinking HR 2.26 (0.76-6.71) Metabolic syndrome + weekly binge drinking HR 4.61 (2.04-10.4)	Age, average alcohol use	Yes	29%

					criteria)				
Younossi, 2019	USA	Longitudinal	4 264 men and women with fatty liver disease (ultrasound) recruited in 1988-1994 (NHANES III)	All-cause death	Reference: No metabolic syndrome + alcohol use ≤3 drinks/day for men or ≤1.5 drinks/day for women Drinker: above these sex-specific limits Metabolic syndrome: yes (Adult Treatment Panel III)	Metabolic syndrome HR 1.32 (1.04-1.68) Drinker HR ? Metabolic syndrome + drinker 3.35 (2.02-5.55)	?	Yes	?

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; OR, odds ratio; GGT, gamma-glutamyltransferase; HR, hazards ratio; HCC, hepatocellular carcinoma

Table 3. Studies analyzing the effects of light-moderate alcohol consumption on steatohepatitis, liver fibrosis, liver cancer or other symptomatic advanced liver disease in subjects with baseline fatty liver disease or metabolic risk.

Author, year, design	Country	Study subjects	Recruitment	Exclusions	NAFLD definition	Assesment of lifetime drinking	Former drinkers	Outcome measure	Adjustments	Effects of light-moderate alcohol use
Dixon 2001, Cross-sectional	Australia	105 bariatric surgery patients	Hospital clinic	History of alcoholism, alcohol > 200 g/wk, hepatotoxic medication, other liver disease	Histology	No	Excluded	Histology	DM, IR	↓ NASH (non-significant after adjusting for diabetes or IR index)
Cotrim 2009, Cross-sectional	Brazil	132 bariatric surgery patients	Hospital clinic	Alcohol use > 280 g/week, other liver disease	Histology	No	n.r.	Histology	-	↑ insulin sensitivity No impact on histology
Ekstedt 2009, Longitudinal	Sweden	71 NAFLD subjects	Hospital clinic	Absent follow-up biopsy (n=20)	Histology	No	n.r.	Histology	Age, sex, BMI, DM, weight gain, HOMA-IR, fibrosis stage at baseline	Binge drinking → ↑ fibrosis progression
Ascha 2010, Cross-sectional	USA	510 cirrhotic patients (195 with NASH)	Hospital clinic	Other liver disease	Histology or radiology	No	Included	HCC	Age, sex, race, BMI, smoking, DM	Any alcohol use: ↑ HCC risk
Dunn 2012, Cross-sectional	USA	582 NAFLD patients (NASH Clinical Research Network)	Hospital clinic	Alcohol use >20 g/day, monthly binge drinking, former drinkers (current abstainers)	Histology	Yes	Excluded	Histology	Age, sex, race, income, education, BMI, exercise, smoking, total calorie intake	↓ NASH (OR 0.56) ↓ ballooning (OR 0.66) ↓ fibrosis (OR 0.56)
Wong 2012, Cross-sectional	Hong Kong	922 adults (264 with fatty liver)	General population	Alcohol consumption ≥ 140 g/week, other liver disease, decompensated liver disease, contraindication for MRI	MRS + US elastography	No	n.r.	MRS + US elastography	Age, sex, MetS	Weak correlation with liver fat content (r=0.11, non-significant) No association with fibrosis.

Sookoian 2014, Cross-sectional	Argentina	414 NAFLD patients	Hospital clinic	n.r.	Histology	No	n.r.	Histology	n.r.	↓ NAFLD and NASH ↓ liver enzymes and inflammatory markers
Kwon 2014, Cross-sectional	USA	77 NAFLD patients	Hospital clinic	History of long-term alcohol abuse or dependence, or >40 g/week, other liver disease, steatogenic medications	Histology	Yes	Excluded	Histology	Age, sex, BMI, % body fat, HOMA-IR, liver enzymes, selected histological features	Alcohol use ≥24 gram-years: less severe disease (OR 0.26)
Kawamura 2016, Longitudinal	Japan	9 959 NAFLD patients	Hospital clinic	Other liver disease, underlying systemic disease, follow-up <48 weeks	US	No	n.r.	HCC	Age, albumin, AST, GGT, platelets, DM, triglycerides, HDL cholesterol	Alcohol use ≥40 g/day: ↑ HCC
Hagström 2017, Cross-sectional	Sweden	120 NAFLD patients	Hospital clinic	Alcohol use > 14 units/week	Histology	Yes	n.r.	Histology	Age, DM, hypertension, BMI, smoking	Lifetime alcohol use up to 13 units/week: ↓ fibrosis
Kimura 2018, Cross-sectional	Japan	301 NAFLD patients	Hospital clinic	n.r.	Histology	No	n.r.	HCC	Fibrosis, diabetes, triglycerides	↑ HCC (RR 4.43, P=0.07)
Mitchell 2018, Cross-sectional	USA	187 NAFLD patients	Hospital clinic	Alcohol use ≥210 g/week (male) or ≥140 g/week (female), other liver diseases, steatogenic medications	Histology	Yes	n.r.	Histology	Age, sex, DM, BMI, HOMA-IR	Alcohol use 1-70 g/wk: ↓ advanced fibrosis (OR 0.33), but only in wine- and non-binge drinkers.
Chang 2019, Longitudinal	South Korea	58 927 adults	Hospital clinic	Alcohol use ≥30 g/day for men or ≥20 g/day for women, other liver disease, steatogenic drugs	US	No	n.r.	Non-invasive fibrosis markers (NFS, FIB-4)	Age, sex, center, screening year, smoking, exercise, education, BMI, DM, hypertension, dyslipidemia, HOMA-IR, hs-CRP	Worsening over time in fibrosis markers

Hajifathalian 2018, Longitudinal	USA	4 568 adults with NAFLD (NHANES)	General population	Alcohol use >3 drinks/day (men) or >2 drinks/day (women), viral hepatitis, increased transferrin saturation	Hepatic steatosis index	No	n.r.	All-cause death	Age, sex, smoking, ethnicity, exercise, education, DM, intake of fiber/polyunsaturated fatty acids	0.5-1.5 drinks/day: ↓mortality (HR 0.64) ≥1.5 drinks/day: ↑mortality (HR 1.45)
Younossi 2019, Longitudinal	USA	4 264 adults with hepatic steatosis (NHANES)	General population	Other liver disease, steatogenic drugs	US	No	n.r.	All-cause death	Age, sex, ethnicity, smoking, MetS,	Alcohol use ≤3 drinks/day (men) or ≤1.5 drinks/day (women): no effect on mortality
Ajmera 2018, Longitudinal	International multicenter	285 NAFLD patients (NASH Clinical Research Network)	Hospital clinic	Alcohol use during 2 years preceding study of >20 g/day (men) or >10 g/day (women), or ≥6 drinks/occasion, other liver disease	Histology	Yes	Excluded	Histology	Age, sex, ethnicity, smoking	Less reduction over time in steatosis grade ↓ NASH resolution (OR 0.32)
Åberg 2019, Longitudinal	Finland	8 345 adults with hepatic steatosis (Health 2000 and FINRISK population surveys)	General population	Alcohol use >50g/day, past drinkers (current abstainers), baseline clinical liver disease, viral hepatitis	Fatty liver index	No	Excluded	- Hospital admission, liver death, liver cancer - All-cause death - Cancer - CVD	Age, sex, BMI, smoking, exercise, DM, marital status, education, employment	↑ liver-related morbidity and mortality, no threshold effect ↑ cancer (↓ CVD) J-shaped association with all-cause death among never smokers

Abbreviations: DM, diabetes mellitus; IR, insulin resistance; NASH, non-alcoholic steatohepatitis; NAFLD, non-alcoholic fatty liver disease; BMI, body mass index; HOMA-IR, homeostatic model assessment for insulin resistance; HCC, hepatocellular carcinoma; MRS, magnetic resonance

spectroscopy; US, ultrasound; MetS, metabolic syndrome; AST, aspartate aminotransferase; GGT, gamma-glutamyltransferase; NFS, NAFLD
fibrosis score; FIB-4, fibrosis-4 index; CVD, cardiovascular disease





